Hormone replacement therapy increases isometric muscle strength of adductor pollicis in post-menopausal women

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A B S T R A C T

A randomized open trial of hormone replacement therapy was used to assess changes in adductor pollicis muscle strength during 6–12 months of treatment with Prempak C 0.625 in comparison with an untreated control group. Muscle strength (maximal voluntary force; MVF), muscle cross-sectional area and bone mineral density were measured. Women entering the trial had oestrogen levels below 150 pmol l⁻¹, confirming their post-menopausal hormonal status. In the treated group, MVF increased by 12.4±1.0% (mean ± S.E.M.) of initial MVF over the duration of treatment, while it declined slightly (2.9±0.9%) in the control group. This increase in strength could not be explained by an increase in muscle bulk, there being no significant increase in cross-sectional area during the study. Those subjects who were weakest at enrolment showed the greatest increases in muscle strength after treatment. Bone mineral density in total hip, Ward’s triangle and total spine increased in the treated group, in agreement with previous studies. There was no correlation between the individual increases in bone mineral density and those in MVF.

INTRODUCTION

We have previously reported a cross-sectional study demonstrating that the pattern of the age-related decline in the specific strength of the adductor pollicis (AP) muscle, i.e. the ratio of its maximum voluntary force (MVF) to its cross-sectional area (CSA), differs in men and women [1]. This thumb muscle has been studied in the clinical setting for over 40 years. Reliable techniques for recording the results of both voluntary and stimulated contractions have been developed over that time [2–5]. We have also developed a simple anthropometric technique for estimating the CSA of the muscle [4], and have shown that interpreting the relationship between measurements of MVF and those of CSA in this small distal fan-shaped muscle is more reliable than in the large multi-pennate proximal muscles of the leg [6].

Adduction of the thumb, allowing grasping movements, is one of the key evolutionary developments from the front foot of lower mammals to the controlled versatility of the primate hand [7]. It is essential for many everyday tasks, from the relatively gross movements required to grip doorknobs and open screw-top jars and bottles, to finer two-handed actions such as dealing with...
small buttons and tying shoelaces. The internal structure of the muscle is highly organized to ensure that optimum tension can be maintained over the wide range of working positions of the thumb [8]. Decline in function simply due to disuse is perhaps less likely in such a muscle than in the large muscles of the lower limb that will be affected to a much greater extent by the overall decline in activity that accompanies aging [9]. AP is also of relatively uniform fibre-type composition (predominantly type I) [10], and thus any effects that might be attributable to age- or hormone-related changes in fibre-type composition are less likely to confuse the interpretation of the results.

In our cross-sectional study, the age-related decline in MVF/CSA of this muscle in men was gradual, starting from about 60 years, whereas in women who were not taking hormone replacement therapy (HRT) there was a sudden decline coinciding with the menopause [1]. This was in contrast with a group of post-menopausal women who were taking HRT, in whom the MVF/CSA of AP was not different from that of pre-menopausal women. Subsequently Greeves et al. [11], in a 9-month longitudinal study found a decline in both maximum dynamic and isometric forces of knee extensors in women not on HRT who were 1–3 years post-menopausal, whereas there was no decline in either measurement in a group of women during the first 9 months of HRT treatment. These results strongly suggest that oestrogen has a role in preserving muscle strength in women. Changes during the menstrual cycle consistent with oestrogen having a muscle-strengthening action have also been described, using the AP [12], maximal hand-grip and quadriceps [13] muscles.

Neither our cross-sectional study [1] nor the longitudinal study of Greeves et al. [11] distinguished between the possibilities (1) that HRT simply maintains muscle strength, if started before the post-menopausal decline occurs, and (2) that it can reverse the decline in those who have become weak through oestrogen deficiency. The fluctuations of muscle strength observed during the menstrual cycle [12,13] suggest that there is potential for at least partial reversibility. A further point that was not addressed by the two longitudinal studies [1,11] is the possibility of selection bias in observational studies. Since it is known that women who take HRT tend to be generally fitter and more active than those who do not [14], an alternative explanation for the observed maintenance of strength in HRT users could be that they were simply a self-selected group of intrinsically stronger women.

We therefore planned a prospective, randomized study of women 5–15 years post-menopause, who we would therefore predict to be weak due to oestrogen deficiency, to investigate whether their weakness could be reversed by HRT. The specific aims of this open, parallel-group trial were (1) to determine if there was any change in AP muscle strength and/or CSA during 1 year’s HRT treatment, (2) to determine the time course for any changes found, and (3) to examine the relationship between any changes in muscle force and in bone mineral density (BMD) that were observed. During the course of this work, two other studies with comparable data have been published [15,16]. Their results will be discussed below in comparison with ours.

**METHODS**

The study medication was Prempak-C® (Wyeth-Lederle). This is a cyclical HRT preparation containing conjugated oestrogens (0.625 mg taken each day) with norgestrel (0.15 mg taken for 12 consecutive days during each 28 day cycle). The treatment was administered for 13 cycles. This dose of conjugated oestrogen is that which is known to increase bone mass [17] and was fixed as part of the trial protocol. We used an open design, because the use of cyclical HRT preparations produces a monthly withdrawal bleed towards the end of the progestogen. Thus a double-blind placebo-controlled experiment is impossible when testing the effects of such a treatment in women who are 10 years post-menopausal. Blinding of the observers was not considered necessary, since objective methods of measurement were used. Also, it is virtually impossible to blind observers in these circumstances, since the subjects have a natural inclination to discuss their symptoms with the observers. The control group received no active intervention, but subjects were offered advice about HRT at the end of the trial.

A total of 122 subjects were recruited to the study by newspaper and radio advertisements. Inclusion criteria were that the subjects were generally healthy women 5–15 years post-menopause, with a serum oestradiol level below 150 pmol l$^{-1}$ and a body mass index of 20–29 kg m$^{-2}$. Subjects gave informed consent to take part in the study, which was approved by the UCL/UCLH Ethical Committee and was carried out in accordance with the Declaration of Helsinki (1989) of the World Medical Association.

As in our earlier studies [1,5], subjects were excluded if they had pain or stiffness of the thumb, evidence of wasting of hand muscles or generalized cardiovascular or neuromuscular disease, or were regularly using any medication likely to affect muscle function or motivation. Additional exclusion criteria for this study were: hysterectomy, undiagnosed genital bleeding, chronic renal or hepatic disease, stroke or transient ischaemic attack, gall bladder disease, known or suspected oestrogen-dependent neoplasia, any other malignancy, known hypersensitivity to oestrogens or progestins, use in the previous 12 months of oestrogen-containing preparations or tibolone, use within the previous 3 years of oestrogen implants, history of glucocorticoid use, blood-clotting
To assess the significance of any differences between the groups, ANOVA was used. Post hoc comparisons between groups were made with Dunnett’s test, with a significance level at 5%. To examine any correlations between different effects of treatment, Pearson correlation coefficients were calculated. Statistical calculations were made with SigmaStat (SPSS Inc, Chicago, IL, U.S.A.).

RESULTS

Table 1 shows the characteristics and initial measurements made on the control and HRT groups. There were no significant differences between the two groups in any of the baseline variables assessed.

In the control group, 48 women completed the trial, 50 remained at 6 months and 52 at 3 months. In the HRT group, 37 completed the trial, 44 remained at 6 months and 48 at 3 months. The higher drop-out rate in the HRT group was due to some subjects experiencing adverse effects of the treatment (heavy withdrawal bleeding with associated discomfort, and weight gain caused by fluid retention), and was to be expected [18]. The diary cards suggested that compliance with the study medication was good (not more than four pills missed per month). The mean results given for each group are those for subjects who completed at least 6 months of the study.

The mean hormone levels demonstrated the expected marked increases with HRT, and are shown in Figure 1. All treated subjects remaining in the study had an increase in oestradiol of at least 50% of their initial level.

To assess the effect of HRT on muscle strength, the measurements of MVF were normalized by dividing each measurement by the overall average strength of that

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<th>Table 1 Characteristics of the subjects entering the study at baseline</th>
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individual subject (see the Methods section). This is because our \textit{a priori} expectation was that any increment would be in proportion to the strength of that individual.

Figure 2(A) shows the changes in normalized MVF, from the start of the trial, as a function of duration of treatment. The treated group showed an increase in muscle strength throughout the period of treatment. Two-way ANOVA showed that the interaction between period of treatment and whether treatment was given was significant \((P < 0.001)\). Post hoc comparisons of normalized muscle strength with initial muscle strength showed a significant increase \((P < 0.05; \text{Dunnett's test})\) at all times from week 4 onwards. At week 52 the difference between the treated and control groups was \(15.4 \pm 1.3\%\) (mean \(\pm\) S.E.M.).

To assess whether the increase in MVF was related to an increase in muscle size, changes in CSA were analysed in the same manner as those of force (Figure 2B). The changes observed were small compared with those of force; the CSA remained within 2\% of its initial value throughout the study in both groups. There were no significant changes compared with the initial value in either group, and there was no significant interaction between time and treatment (two-way ANOVA; \(P = 0.46\)). The mean increase in CSA in the treated group was significantly less than the increase in force.

The ratio of MVF to CSA was also examined statistically. Figure 3 shows the ratio of these quantities (without any normalization) as a percentage of its initial value.
Hormone replacement therapy increases muscle strength

Figure 4 Individual trends in muscle strength during the study plotted against the initial MVF
(A) HRT group; (B) control group. The solid lines are the regression lines, and broken lines indicate 5% confidence limits for the population.

value. The ANOVA analysis showed significant effects of both time and treatment, and a significant interaction \((P < 0.001)\). The differences in MVF/CSA between the two groups was significant from week 26 \((P < 0.05;\) Dunnnett’s test).

In order to examine whether any of our measured variables might predict the increase in MVF in individual subjects, we calculated the extent to which each subject’s MVF changed during treatment. For this purpose we used only those 39 subjects who completed 39 or more weeks of the trial. Since the mean change in muscle strength increased throughout the year of HRT, this was done by taking the slope of the linear regression of MVF measurements against duration of treatment. In the control group 20 subjects showed a positive slope (increase in muscle strength) and 29 showed a negative slope. In the HRT group, muscle strength increased in 36 subjects and decreased in three. The difference in the numbers of subjects showing a positive slope in the HRT and control groups was significant in a Chi-squared test \((P < 0.0001)\). The following variables were examined to see whether they were correlated with the individual trends in MVF: initial MVF, age, years post-menopause, initial level of oestradiol, initial level of oestrone, increase in oestradiol, increase in oestrone, and body weight. Of these, only initial MVF \((r = -0.522)\) and initial oestrone \((r = 0.378)\) showed significant correlations. The correlation with initial MVF is illustrated by the scatter diagrams in Figure 4. However, a multiple regression model using these two variables could explain only 34\% of the variance between individuals in the increase in MVF during the year of treatment \((i.e. r^2 = 0.341)\).

The BMDs of the hip and the spine were measured at the initial screening, and after 6 and 12 months of the study. The initial measurements are in Table 1. In order to assess changes over the course of the study, each BMD measurement was expressed as a fraction of the initial measurement at the same site. These normalized results are shown in Figure 5. ANOVA showed that HRT had significant effects \((P < 0.05;\) Dunnett’s test) at all sites except the neck of femur, which were apparent both at 26 and at 52 weeks. Individual improvements in BMD were averaged for the three sites at which there were mean improvements. There was no correlation between these individual improvements in BMD and those in MVF \((r = -0.011)\).

Over the 1 year of the trial, the mean body weight of the subjects remained within 98–102\% of the initial value, and there were no significant changes in either the control or HRT groups.

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DISCUSSION

We have shown that giving HRT to women 5–15 years after their menopause results in a 15.4 ± 1.3% (mean ± S.E.M.) increase in the isometric MVF of AP compared with the control group. Those who were weakest to start with benefited most. Figure 2 shows an approximately continuous rise in MVF during the whole year of treatment. The increase in MVF did not appear to reach a plateau within this time. This contrasts with the hormone levels, which, as expected, stabilized soon after treatment began. It is important to note that the study group was selected as having oestriadiol levels below 150 pmol·l⁻¹, and that they all showed a clear increase in hormone levels on treatment. The fact that, on average, they achieved increases in BMD comparable with those in previous reports [17] also demonstrates that they responded to HRT in the predicted fashion.

Two previous longitudinal studies [15,16] have reported on the effect of HRT administration on muscle strength. Both of these studies used similar doses of oestrogen to that in our study and were of a similar duration to ours. The study by Armstrong et al. [15] tested the effects of HRT administration on various parameters, including maximal grip and leg extensor power, in a group of women aged 45–70 years who had sustained a distal radius fracture within the previous 3 months. On average, no increase in muscle strength was found after 1 year’s treatment with HRT. However, many of the subjects had initial oestriadiol measurements well in excess of the accepted post-menopausal range and many subjects failed to show a clear increase in oestriadiol level after HRT treatment. Thus, in order to compare the results from that study with ours, in which only subjects whose oestriadiol measurements were below 150 pmol·l⁻¹ were enrolled, and in which all subjects showed a clear increase in hormone levels on treatment, it is necessary to consider only those among Armstrong et al.’s subjects who did show an increase in oestriadiol levels during treatment. This can be done from the data in Figure 1 of their paper, which shows that, for the 23 subjects whose oestriadiol increased by more than 50%, there was a significant increase in grip strength by 5.5 ± 2.3% (mean ± S.E.M.; P = 0.024). This increase, which was not noted by the authors, is less than that we report; this is probably because the increases in oestrogen concentration in our study were larger. It is worth noting that the analysis of Armstrong et al. [15] includes all subjects recruited to the treatment group, 21% of whom did not comply with the medication, whereas our analysis is based on those subjects remaining in the trial at the relevant time point (26% had withdrawn from the treatment group by the end of the trial).

The other longitudinal study, by Kohrt et al. [16], used only 32 subjects, divided between four groups, to test whether additive effects of weight-bearing exercise and HRT could be seen in groups of women aged 60–72 years not accustomed to either. During this investigation, 23–26% increases in averaged peak torque during isokinetic movements of the knee extensors were achieved in the ‘exercise’ and ‘exercise + HRT’ groups. However, HRT conferred no additional benefit compared with exercise alone and, in the ‘HRT alone’ group no increase in torque was observed during the treatment. Combining the two estimates in the work of Kohrt et al. [16] gives a result for the effect of HRT on torque of −5.5 ± 6% (mean ± S.E.M.). This differs significantly from our measurements of muscle strength, but there are important differences in the experiments. Firstly, we measured force during isometric muscle contractions, while Kohrt et al. [16] measured torque during isokinetic contractions. This torque measurement depends on the intrinsic speed of the muscles as well as on their intrinsic strength. The potential for oestrogen to change speed of contraction is unknown, but it is entirely possible that the maximum isokinetic torque might not increase in line with isometric strength during oestrogen treatment. Secondly, the rises in BMD observed during Kohrt et al.’s study [16] were generally lower than in ours, suggesting that their subjects may have been less responsive to HRT as a group.

Although there was no significant effect of age in our subjects, whose age range was 53–67 years, the fact that Kohrt et al.’s subjects [16] were older than ours, with average ages of 65–67 years across the four groups, may also be important, especially as aging is known to have differential effects on speed and force of contraction [19].

Two other studies have failed to show any benefit of HRT on muscle in older women. In one [20], no difference in lower body strength was found between 37 women on HRT (average age 68.4 years) and 48 who had never had HRT (average age 69.9 years). Again, differences in BMD between the two groups were small. An isotonic one repetition maximum method was used to measure strength. This is another measurement that depends on speed as well as force of contraction, and additionally has a large learning component [19].

The other study of older women [21] involved the participation of over 9000 non-black Americans, who were divided into current HRT users (average age 70.2 years), past users (average age 70.8 years) and those who had never had HRT (average age 72.4 years). Hand-held dynamometry was used to assess strength, and no differences were found between the three groups for grip strength. Since multiple centres participated, there was obvious potential for inter-observer variation in these measurements, and it is puzzling that the values given for the most powerful muscle group measured, the hip abductors, are about half those for grip. This makes it hard to evaluate the finding that hip abductor strength was actually lower in the current HRT users than in the other two groups. It is also puzzling that although, as expected, the women on HRT were generally fitter [14],
of the contracting muscle. The only simple interpretation of post-menopausal and pre-menopausal women [24]. In declination in AP muscle strength by our earlier comparison however, excluded as an explanation for the menopausal ractile tissue within the muscle. That explanation was, change the amount of non-contractile relative to cont-

possibility that the effect of oestrogen in this study was to CSA, but not of force. We cannot altogether exclude the connective tissue, that contribute to the measurement of changes in the muscle structure, such as increases in muscle strengthening reported here, are too rapid to be due to changes in the ratio of connective tissue to muscle tissue. We therefore consider it likely that the change ultimately produced in the muscle as a result of HRT is at the level of the cross-bridge [25]. However, the exact nature of the intervening processes between oestrogen ingestion and a change in MVF, without a change in CSA, is at present unknown.

In conclusion, our study is the first randomized trial in which isometric muscle strength has been measured in patients in whom HRT elevated oestrogen from initial post-menopausal levels and who responded to HRT with the expected changes in BMD. We have found an extremely clear increase in muscle strength over a treatment period of 1 year that is large enough to be likely to have beneficial functional consequences for those who are able to tolerate the treatment. Those who were weakest benefitted most.

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